Papers and Originals

Folate Deficiency in Crohn's Disease: Incidence, Pathogenesis, and Treatment

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Megaloblastic anaemia due to folate deficiency is a well-recognized complication of idiopathic steatorrhoea and acute tropical sprue. These conditions are characterized by abnormalities of mucosal structure and absorptive function of the proximal small intestine, the principal site of folate absorption. On the other hand, in patients with anatomical lesions of the small intestine such as blind loops, strictures, and ileal resections, megaloblastic anaemia, if it occurs, is almost invariably due to vitamin B_{12} deficiency (Mollin, 1960).

Nevertheless there are a few reports which suggest that severe folate deficiency, sometimes with megaloblastic anaemia, may occur in patients with Crohn's disease. Klipstein (1963) found an extremely low serum folate level in one patient with this disease which he attributed to inadequate dietary intake of the vitamin. Rose (1965) found subnormal serum folate levels in a further three patients, two of whom showed "transitional" megaloblastic changes and one of the latter also excreted raised amounts of formiminoglutamic acid (Figlu). The patient of Hall (1953) who developed megaloblastic anaemia which responded to large doses of folic acid, and the four anaemic patients of Knowles (1962) with positive Figlu tests, may also have been suffering from folate deficiency; but neither of these studies is conclusive, since B_{12} deficiency, which could have equally well been present, was not excluded. Thompson and Ungley (1955) describe the case of a patient who, though not anaemic, was suffering from diarrhoea and loss of weight while on treatment with vitamin B_{12}, which were promptly improved when folic acid was given. Though no direct tests for folate deficiency were available, it is likely that this patient suffered from such deficiency.

In our experience folate deficiency is frequent in patients with active Crohn's disease, and the purpose of this paper is to report the incidence and pathogenesis of the deficiency in a group of 64 patients and describe the value of folic acid therapy in this condition.

Subjects Studied

Patients with Crohn's Disease

Observations were made on 64 patients (Table I) with Crohn's disease (27 males and 37 females), their ages ranging from 8 to 67 (mean 34.5) years. In 40 of the patients the diagnosis had been confirmed at laparotomy before the present studies were made, and in a further seven the diagnosis was confirmed when they subsequently came to laparotomy. In the remaining 17 the diagnosis was made because the patients suffered from abdominal pain, diarrhoea, loss of weight, and fever, and showed characteristic narrowing with or without ulceration of the ileum on barium follow-through examination.

The clinical histories of the patients ranged from a few months to 25 years. Twenty-four were in hospital and 40 were attending hospital as outpatients or were under the care of their general practitioner. Ten of the 64 patients were already receiving regular parenteral B_{12} therapy (200 μg. monthly) for previously diagnosed megaloblastic anaemia due to B_{12} deficiency.

TABLE I.—*Peripheral Blood Findings in the 64 Patients, Showing the Number of Patients in Each Clinical Group with Anaemia, Macrocytes, and Hypersegmented Polymorphs*

	Group 1			Group 2			Group 3		
	No. of Cases	No. (%) Macrocytic	No. (%) H-S. P.	No.	No. (%) Macrocytic	No. (%) H-S. P.	No.	No. (%) Macrocytic	No. (%) H-S. P.
Anaemic ..	2	0	0	8	5 (62)	5 (62)	18	12 (67)	9 (50)
Non-anaemic	19	1 (5)	1 (5)	13	2 (15)	3 (23)	4	1 (25)	2 (50)
Total ..	21	1 (5)	1 (5)	21	7 (33)	8 (38)	22	13 (59)	11 (50)

H-S. P. = Hypersegmented polymorphs.

The patients were divided into three groups according to the severity of their symptoms, without foreknowledge of the results of the study.

Group 1.—Patients who were clinically well and symptomless or who had no symptoms that could be attributed to Crohn's disease.

Group 2.—Patients who were unwell with symptoms that could be ascribed to Crohn's disease. These patients needed regular medical attention, but their symptoms were not severe enough to prevent them from working or to warrant admission to hospital.

Group 3.—Patients who were severely ill, the majority confined to bed, and all in hospital or requiring admission to hospital.

The mean ages of the patients from groups 1, 2, and 3 were 38.6, 33.7, and 30.3 years respectively.

Control Group

The control group was made up of 50 adult hospital outpatients (25 males and 25 females) selected at random except that antenatal patients and patients known to be anaemic or to be suffering from gastrointestinal or malignant disease were excluded. Their ages ranged from 17 to 83 (mean 49) years.

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Methods

Serum folate levels were determined by microbiological assay with *Lactobacillus casei* as test organism by the method of Waters and Mollin (1961). The normal range is from 6 to 21 mμg./ml.

Red cell folate levels were measured by the modification of the serum folate assay described by Hoffbrand *et al.* (1966b) in which venous blood is haemolysed in distilled water containing 1 g. of ascorbic acid per 100 ml. before assay. The normal range is from 160 to 640 mμg./ml. of packed red cells.

Figlu and urocanic acid were measured by the spectrophotometric method of Chanarin and Bennett (1962a) in an eight-hour urine specimen collected after an oral dose of 15 g. of L-histidine monohydrochloride. The normal range for Figlu excretion is from 0 to 17 mg. in eight hours. Urocanic acid excretion of 17 mg. or less in the eight-hour period is also regarded as normal (Hoffbrand *et al.*, 1966a).

Serum vitamin B_{12} levels were determined by microbiological assay with the "z" strain of *Euglena gracilis* as test organism (Anderson, 1964). The normal range is from 160 to 925 μμg./ml.

Folic acid absorption was measured by microbiological assay with *Streptococcus faecalis* as test organism as described by Chanarin *et al.* (1958). In normal subjects the peak serum folate level after the standard oral dose of folic acid (40 μg./kg. body weight) is more than 40 mμg./ml.

Dietary folate intake was calculated by use of standard tables (McCance and Widdowson, 1960). So far as possible, allowance was made for loss of folate in cooking.

Routine haematological methods were those described by Dacie and Lewis (1963). Stained peripheral blood films were examined for the presence of macrocytes and hypersegmented polymorphs (one or more polymorphs with six or more nuclear lobes per 100 polymorphs). Bone marrows were classified as normoblastic or megaloblastic. The megaloblastic marrows were further subdivided into (1) those showing mild changes (rare intermediate megaloblasts and occasional giant metamyelocytes, and (2) those showing intermediate changes (Dacie and White, 1949). Florid megaloblastic changes as occur in severe untreated Addisonian pernicious anaemia were not seen.

Results

Serum B_{12} Concentrations.—The serum B_{12} levels of 51 of the 54 patients not already receiving regular B_{12} therapy were normal, ranging from 160 to 825 (mean 373) μμg./ml. In the other three patients the levels were subnormal (125, 130, and 130 μμg./ml.) but not as low as usually occurs in untreated pernicious anaemia.

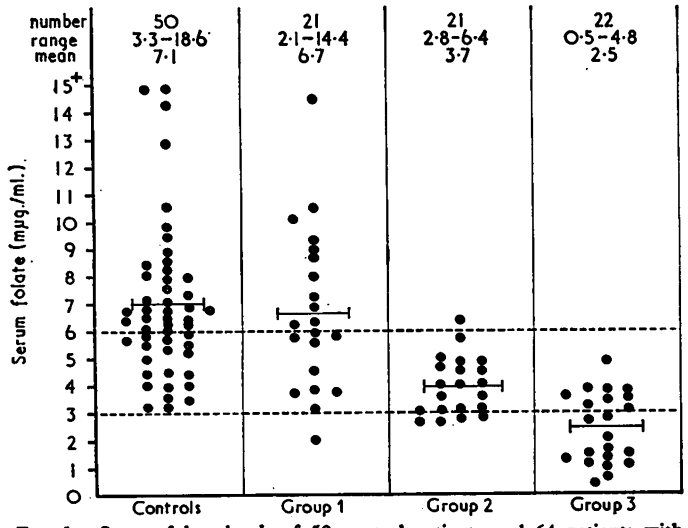

FIG. 1.—Serum folate levels of 50 control patients and 64 patients with Crohn's disease. The latter are divided into three clinical groups (see text). The upper horizontal line is the lower limit of the range of serum folate levels in normal subjects. The lower horizontal line is the lower limit of the control serum folate levels.

Serum Folate Concentrations.—Of the control subjects 21 (42%) had subnormal serum folate levels—that is, less than 6 mμg./ml.—but all were above 3 mμg./ml. In contrast, as many as 52 (81%) of the patients with Crohn's disease had subnormal serum folate levels and 18 (28%) had levels less than 3 mμg./ml. (Fig. 1). Serum folate levels below the control range occurred most frequently in the patients with the most active disease. Thus 13 of the severely ill patients (group 3) had serum folate levels less than 3 mμg./ml. compared with only 4 of the less severely ill patients (group 2) (Fig. 1). Only one of the symptom-free patients (group 1) had such a low level. On the other hand there was no relation between serum folate level and the age or sex of the patients, length of history, or whether or not the patients had had an operation for the disease.

Red Cell Folate Concentrations.—Subnormal red cell folate levels occurred in five of seven severely ill patients tested, in two of eight mildly ill patients, but in none of four symptom-free patients.

Figlu Excretion.—This was measured in 24 patients, all of whom had normal serum B_{12} levels. Like subnormal serum and red cell folate levels, positive Figlu tests occurred most often in the patients with the most active disease (Fig. 2). Thus Figlu excretion was raised in all 10 severely ill patients tested, in only two of nine less severely ill patients, and in none of five symptom-free patients.

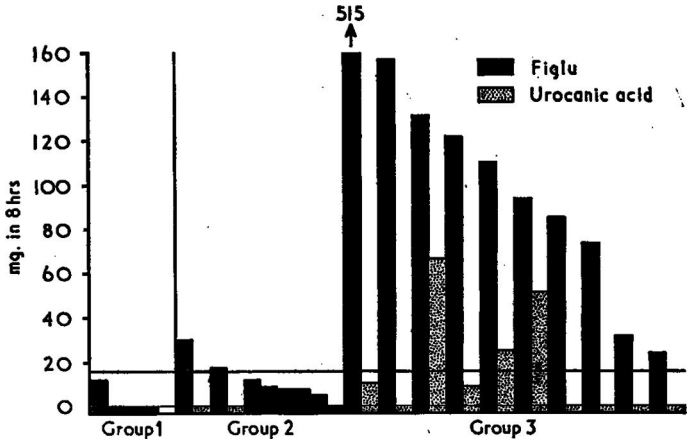

FIG. 2.—Excretion of Figlu and urocanic acid in 24 patients with Crohn's disease. The horizontal line denotes the upper limit of the normal range of Figlu excretion and the upper limit of the normal range of urocanic acid excretion.

Urocanic Acid Excretion.—This was raised in three of the 10 severely ill patients with positive Figlu tests, but was normal in the other 21 patients tested (Fig. 2).

Haematological Findings

Peripheral Blood.—Anaemia was present in 28 of the patients (Table I). The anaemic patients were generally severely ill with multiple causes of anaemia—for example, active inflammatory disease, iron deficiency, etc. They usually required urgent therapy with steroids, antibiotics, iron, transfusions, etc., so it was difficult to observe the effect of folic acid therapy alone, and therefore impossible to estimate in how many of the 28 patients folate deficiency contributed to anaemia. There was, however, an obvious association between the presence of anaemia and presence of haematological changes due to folate deficiency in the peripheral blood. Thus macrocytosis and/or

hypersegmented polymorphs, like anaemia, occurred far more often in the severely ill patients than in those without symptoms (Table I). Moreover, macrocytosis was seen in the films of 17 of the anaemic patients but in the films of only 4 of the non-anaemic patients; and hypersegmented polymorphs occurred in 14 of the anaemic and only 6 of the non-anaemic patients. Macrocytosis and hypersegmented polymorphs could almost certainly be ascribed to folate deficiency, since all but one of the patients showing these features had subnormal serum folate and normal serum B_{12} levels. The remaining patient had subnormal serum folate and serum B_{12} levels (2.7 mμg./ml. and 130 μμg./ml. respectively).

Bone Marrow.—Bone marrow examinations were performed in 17 anaemic and six non-anaemic patients (all with normal serum B_{12} levels (Table II). The marrow showed megaloblastic changes in 12 anaemic and three non-anaemic patients. Like other evidence of folate deficiency, megaloblastic changes were particularly frequent in the patients with the most active disease (Table II).

All 15 patients with megaloblastic changes had subnormal serum folate levels, and in 11 these were less than 3 mμg./ml. Of the patients with normoblastic erythropoiesis four had subnormal serum folate levels, but these were invariably above 3 mμg./ml. Surprisingly, two patients with normoblastic haemopoiesis had positive Figlu tests, usually indicating severe folate deficiency.

Results of Folic Acid Therapy

It was possible to study the effect of folic acid therapy in seven patients (four with intermediate megaloblastic changes and three with mild megaloblastic changes). None of them showed a complete haematological remission on folic acid treatment alone. The best response occurred in one of the severely ill patients (Case 13, Table II).

This patient had suffered from Crohn's disease for four years and was admitted to the hospital with a four-month history of increasing anorexia and diarrhoea. He was anaemic (haemoglobin 6.6 g./100 ml., P.C.V. 20%, red cell count 1,700,000/cu. mm., reticulocytosis 0.5%, white cell count 5,000/cu. mm., platelets 150,000/cu. mm.). The stained peripheral blood film showed obvious macrocytosis and hypersegmented polymorphs, and the bone marrow showed intermediate megaloblastic changes with adequate iron stores but siderotic granules almost completely absent from the developing erythroblasts, indicating defective iron utilization.

He was transfused with the packed cells from 2 pints (1,140 ml.) of blood and then given folic acid (15 mg. intramuscularly daily). There was a reticulocytosis to a peak of 13% with a slow rise of haemoglobin to 12 g./100 ml. and a rise in leucocytes from normal to supranormal levels (Fig. 3). Both the

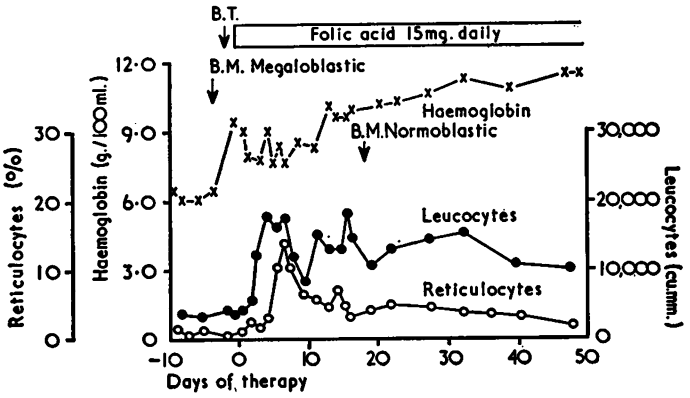

FIG. 3.—Haematological response of one patient (Case 1) to folic acid.

haemoglobin and leucocyte count became normal when the patient was subsequently treated with A.C.T.H. (40 units daily) and sulphasalazine (1 g. t.d.s.).

Two further patients (Cases 2 and 12, Table II) with intermediate megaloblastic change due to folate deficiency and initial haemoglobin concentrations of 8.9 and 11.9 g./100 ml. showed significant reticulocyte responses and increases in haemoglobin of 3.1 and 2.0 g./100 ml. respectively with folic acid therapy (15 mg. daily by mouth). On the other hand four mildly anaemic patients (Cases 3, 9, 15, and 16, haemoglobin range from 10.4 to 13.0 g./100 ml.) showed no definite haematological response to folic acid in large doses. However, all seven patients treated with folic acid showed striking subjective improvement, increased appetite, and gain in weight.

Pathogenesis of the Folate Deficiency

There are three possible causes for folate deficiency in Crohn's disease: malnutrition, malabsorption, and excess folate utiliza-

TABLE II.—*Detailed Haematological and Biochemical Findings in the 23 Patients on whom Bone Marrow Examinations were Performed.*

Case No.	Sex	Hb (g./100 ml.)	Peripheral Blood		Bone Marrow		Serum B_{12} (μμg./ml.)	Serum Folate (mμg./ml.)	Red Cell Folate (mμg./ml.)	Figlu (mg./8 hrs.)	Urocanic Acid (mg./8 hrs.)	Calculated Daily Folate Intake (μg.)	Folic Acid Absorption (mμg./ml.)		
			Macrocytosis	H-S. P.	M-G.-G.*	Iron							0 hr.	1 hr.	2 hrs.
							Group 3								
1	M	6·6	+	+	Int. meg.	Present	255	0·5	39	110	25	24	0	64	43
2	F	8·9	+	+	Int. meg.	Present	Rec. B_{12}	1·1	53	—	—	—	0	34	36
3	F	10·7	+	+	Int. meg.	Present	165	4·8	122	28	0	33	0	97	92
4	M	12·2	+	+	Int. meg.	Absent	330	3·8	—	515	8	—	0	9	15
5	M	10·8	+	−	Mild meg.	Present	260	3·6	88	158	0	—	—	—	—
6	M	12·6	+	−	Mild meg.	Present	465	2·0	103	85	0	—	—	—	—
7	M	13·0	+	+	Mild meg.	Present	190	1·6	—	121	9	—	—	—	—
8	F	7·4	−	−	Mild meg.	Absent	640	2·3	—	22	0	24	0	9	78
9	M	10·4	−	+	Mild meg.	Absent	235	2·6	—	74	0	—	—	—	—
10	F	9·6	−	+	Normo	Absent	Rec. B_{12}	3·5	250	94	49	38	0	39	40
11	F	10·0	−	−	Normo	Absent	700	7·8	240	131	65	49	0	57	73
							Group 2								
12	M	11·9	+	+	Int. meg.	Present	Rec. B_{12}	3·2	111	18	0	200	0	16	127
13	F	14·7	+	+	Int. meg.	Present	175	4·8	126	30	0	56	0	30	49
14	M	13·3	+	+	Mild meg.	Present	Rec. B_{12}	3·3	237	12	0	86	0	> 100	> 100
15	M	13·0	−	+	Mild meg.	Present	265	3·8	313	8	0	72	0	42	45
16	M	12·0	+	−	Mild meg.	Absent	825	3·2	198	0	0	—	—	—	—
17	F	12·1	−	+	Mild meg.	Present	300	4·6	185	9	0	77	0	9	8
18	M	15·5	−	−	Normo	Present	Rec. B_{12}	3·6	230	6	0	53	0	10	30
19	F	12·6	−	−	Normo	Absent	320	2·9	307	8	0	86	0	32	43
							Group 1								
20	M	13·9	−	−	Normo	Present	Rec. B_{12}	7·1	369	11	0	—	0	67	54
21	F	12·3	−	−	Normo	Present	305	5·6	457	—	—	—	0	78	85
22	F	11·2	−	−	Normo	Absent	215	8·7	601	0	0	—	—	—	—
23	F	11·3	−	−	Normo	Absent	370	8·0	533	0	0	—	—	—	—

* May-Gruenwald-Giemsa stain. Mild meg.=Mild megaloblastic. Int. Meg. = Intermediate megaloblastic. H-S.P=Hypersegmental polymorphs.

tion. In some of the patients it was possible to investigate folic acid absorption and dietary folate intake.

Folic acid absorption was subnormal in 4 out of 16 patients tested (Table II). Three of the four (Cases 4, 17, and 18) with subnormal absorption had radiological evidence of duodenal and/or jejunal involvement by the disease. In the fourth (Case 2) there was active disease with no radiological evidence of proximal intestinal involvement.

Dietary folate intake was assessed in 12 of the 16 patients in whom folic acid absorption tests were performed (Table II). The calculated intake was normal in six mildly ill patients, including four in whom the absorption of folic acid was normal though they had biochemical and haematological evidence of folate deficiency. In contrast, the calculated folate intake was inadequate in all five severely ill patients questioned (Table II). Inadequate intake of folate therefore appeared to be an important factor contributing to the deficiency in the severely ill patients, but in the patients with less active disease neither poor diet nor malabsorption appeared to be a major factor in causing the deficiency.

Effect of Therapy for Crohn's Disease on Folate Status of Patients in Group 3

Three patients with Crohn's disease who were admitted to hospital acutely ill with anorexia, fever, loss of weight, abdominal pain and diarrhoea were found to be severely folate-deficient (Cases 5, 6, and 7, Table II). Throughout their treatment for Crohn's disease they received no folic acid, but the changes in their folate status were followed during treatment of the primary disease. Radiological studies showed evidence of Crohn's disease of the terminal ileum in each patient. All three were anaemic with normal serum B_{12} levels but subnormal serum folate levels and raised Figlu excretion (Fig. 4). Despite this biochemical evidence of severe folate deficiency the bone marrows showed only mild megaloblastic changes. They also showed normal iron stores but a reduced number of siderotic granules in the developing erythroblasts. Initially each patient was given oral prednisone (from 20 to 60 mg. daily) but did not respond. Subsequently each patient was treated surgically by an ileocolostomy bypass.

Postoperatively, all three patients were clinically improved, with a gain in appetite and in weight and subsidence of abdominal symptoms. The signs of folate deficiency progressively diminished, and six months after operation they showed only minimal or no evidence of the deficiency (Fig. 4). Figlu tests were normal; macrocytes were absent from the peripheral blood, and the bone marrows were normoblastic. Anaemia was cured in two patients, and the residual anaemia in Case 5 responded to iron therapy alone. The serum folate levels in each patient had risen substantially, but these were still subnormal in Cases 6 and 7 (5.2 and 5.0 mμg./ml. respectively).

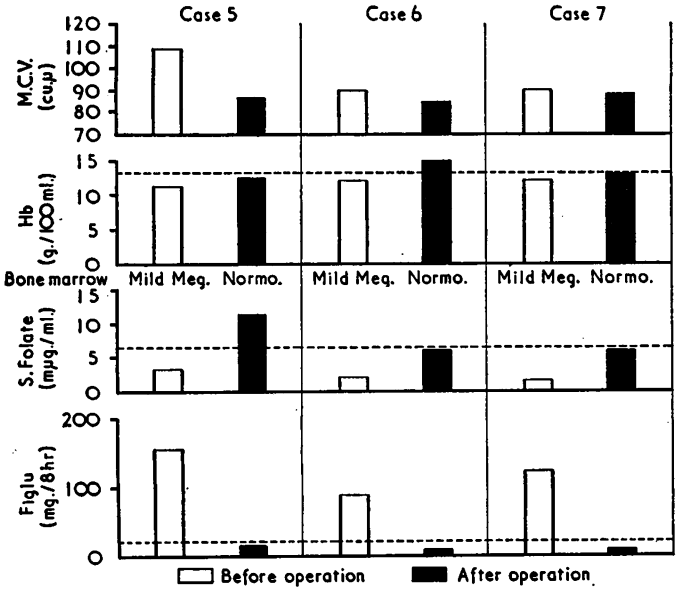

FIG. 4.—Preoperative and six-month postoperative haematological and biochemical findings in three patients (Cases 5, 6, and 7) whose folate deficiency regressed after successful ileal bypass.

Discussion

Evidence of Folate Deficiency

The results of this study show that megaloblastic anaemia due to folate deficiency occurs in a small proportion of patients with active Crohn's disease. In addition they show that less severe deficiency occurs in a considerable proportion of such patients.

There was both haematological and biochemical evidence of the deficiency, and usually a good correlation was found between the occurrence of these haematological changes (macrocytosis, hypersegmented polymorphs in the peripheral blood, and megaloblastic marrow changes) and biochemical changes (subnormal serum and red-cell folate levels and positive Figlu tests) among the patients. However, positive Figlu tests which suggest reduced tissue folate concentrations (Herbert, 1962; Chanarin *et al.*, 1966; Hoffbrand *et al.*, 1966b) occurred in several patients with only mild megaloblastic changes or even normoblastic haemopoiesis. Folate deficiency, however, is not the only cause of positive Figlu tests. Liver disease may cause raised Figlu excretion in the absence of folate or in B_{12} deficiency; and it is possible that in some patients positive Figlu findings were due to direct impairment of liver function by Crohn's disease itself. Conventional liver-function tests were not performed routinely, but the finding of raised urocanic acid excretion in three of the patients whose Figlu tests were positive does suggest impaired liver function (Hoffbrand *et al.*, 1966a). A second explanation for the discrepancy is that active inflammation may have masked megaloblastic change by causing defective iron incorporation into erythroblasts.

Pathogenesis of the Deficiency

Folate deficiency in these patients was probably caused by a combination of three factors: poor diet, malabsorption, and excess demands for the vitamin. Inadequate dietary intake was certainly present in patients with severe disease. However, even in some of these patients folate intake was not low enough in itself to cause the severe deficiency from which they suffered. Thus only two of the severely deficient patients questioned had intakes within the range Gough *et al.* (1963) found in patients with nutritional megaloblastic anaemia—that is, less than 25 μg. daily. In other folate-deficient patients the calculated folate intake was well within the normal range.

Malabsorption of folate may have been a contributing factor in some of the patients. This is known to occur in patients with Crohn's disease with duodenal or jejunal involvement (Chanarin *et al.*, 1958; Cox *et al.*, 1958; Chanarin and Bennett, 1962b; Klipstein, 1963, 1966). In the present study malabsorption of folic acid was also demonstrated in patients with involvement of the proximal small intestine. In the majority of the folate-deficient patients studied here, however, the disease appeared to be confined to the ileum, and in all except one of these patients tested, and in patients in whom the ileum had been bypassed, folic acid absorption was normal. Experiments, the findings of which are given in Table III, suggest that folic acid is not significantly absorbed from the lower ileum. Folic acid was instilled direct into the ileum in two subjects. The absorption, measured microbiologically and by radioactivity, was slightly less from the upper ileum than when the dose was given by mouth, but no absorption could be detected from the lower ileum.

TABLE III.—*Comparison of the Absorption of Folic Acid in Two Normal Subjects (A and B) and One Patient with Untreated Idiopathic Steatorrhoea (C) When the Dose was Given (a) by Mouth and (b) by Direct Instillation Into the Small Intestine. Each Dose was 40 µg. Folic Acid/kg. Body Weight Labelled with 20 µCi Tritium, and the Absorption was Determined by the Rise in Serum Folic Acid Measured by* Str. faecalis *Microbiological Assay and by the 24-hour Urinary Excretion of Radioactivity After a 15-mg. Intramuscular Flushing Dose of Non-radioactive Folic Acid Administered Three Hours After the Oral or Intestinal Dose*

Case	Distance of Tip of Small Intestinal Tube From Incisor Teeth (cm.)	Radiological Position of Tip of Small Intestinal Tube	Site of Administration of Folic Acid	Serum Folate Levels (Hours)				Urinary Excretion Radioactivity in 24 hours (%) (Normal >30%)
				0	1	2	3	
A	—	—	Oral	0	105	82	48	35·0
	170	Lower jejunum	Lower jejunum	0	66	63	40	30·2
B	—	—	Oral	0	98	77	56	45·6
	250	Mid-lower ileum	Mid-lower ileum	0	3	1	0	0·0
C	—	—	Oral	1	23	34	31	—
	200	Upper ileum	Upper ileum	0	18	51	24	—

One severely ill patient (Case 2) did malabsorb folic acid even though her disease was apparently confined to the terminal ileum. This suggests that extremely active disease of the ileum might affect jejunal function. However, in other patients with extremely active disease of the ileum folic acid absorption was normal (Table II).

The third factor of possible importance in the pathogenesis of the deficiency is increased folate utilization due to the active inflammatory disease. Inflammation may provoke folate deficiency in the experimental animal (May *et al.*, 1952) and in patients with rheumatoid arthritis (Gough *et al.*, 1964) and tuberculosis (Roberts *et al.*, 1966). In these conditions the deficiency is presumably caused by increased folate requirements due to increased production of granulocytes and other inflammatory cells. In active Crohn's disease there is likely to be increased folate utilization from this cause. Since dietary folate intake and folic acid absorption were both well within the normal range in some patients with folate deficiency, in these patients, at least, increased utilization was likely to be a major factor in causing the deficiency.

Value of Folic Acid Therapy

It was impossible to estimate to what extent folate deficiency contributed to anaemia among these 64 patients. There was a significant though incomplete haematological response to folic acid in three anaemic patients with intermediate megaloblastic changes. All seven deficient patients given folic acid showed marked subjective improvement, with a prompt gain in appetite and weight. It would therefore seem advisable to treat with folic acid all patients with active Crohn's disease and haematological and biochemical changes due to the deficiency. The incidence of patients needing folic acid therapy is likely to be high among those with severely active disease.

Vitamin B_{12} deficiency, which causes haematological changes identical to folate deficiency, also occurs frequently in patients with Crohn's disease, particularly after ileal resection. Before giving folic acid therapy to patients with Crohn's disease it is therefore essential to exclude B_{12} deficiency—for instance, by measuring the serum B_{12} level—in order to avoid precipitating neurological damage.

As shown in the three patients studied here, before and after surgical intervention, folate deficiency may also be corrected by successful treatment of the Crohn's disease without folic acid therapy. In these three patients the diet improved postoperatively, and presumably the intake of folate increased and the demands for the vitamin diminished. Spontaneous remission of a macrocytic anaemia in Crohn's disease after successful operation was recorded by Butt and Watkins (1936). They did not establish the cause of the macrocytic anaemia in their patients, but the phenomenon they observed is probably the one recorded in these three patients here.

Summary

In the present study of 64 patients with Crohn's disease a high incidence of folate deficiency was found among patients in the active stage of the condition. Haematological changes due to the deficiency included macrocytosis and hypersegmented polymorphs in the peripheral blood and megaloblastic changes in the bone marrow. Biochemical changes included low serum and red cell folate levels and positive Figlu tests. Vitamin B_{12} deficiency was excluded as a cause of these changes in all but one patient.

Folate deficiency appeared to be due to a combination of factors—inadequate dietary intake, excess utilization, and malabsorption of the vitamin. There was a marked subjective improvement and gain in weight in all seven folate-deficient patients given folic acid therapy and definite haematological improvement in the three with the most severe deficiency. Folate deficiency in three patients with active Crohn's disease remitted spontaneously after successful surgical therapy of the Crohn's disease itself. It is concluded that severe folate deficiency is a frequent complication of active Crohn's disease and that folic acid therapy may prove beneficial in a high proportion of such patients.

Because of the high frequency of B_{12} deficiency in Crohn's disease, however, it is always essential to exclude this before giving folic acid. Folate deficiency in Crohn's disease may be cured slowly without folic acid therapy, by successful treatment of the Crohn's disease itself.

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